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Original articles

Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies

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The results of a combined analysis and separate analyses of four multicenter, randomized, parallel group studies that evaluated the effects of once-daily topical administration of becaplermin gel for the treatment of chronic, full thickness, lower extremity diabetic ulcers are presented. The four studies included a total of 922 patients with nonhealing lower extremity diabetic ulcers of at least 8 weeks' duration. Following initial complete sharp debridement of the ulcer, patients were randomized to receive a standardized regimen of good ulcer care alone, good ulcer care plus placebo gel, or good ulcer care plus becaplermin gel-30 μg/g, or good ulcer care plus becaplermin gel-100 μg/g, with various combinations of regimens used in the four studies. Safety was assessed by monitoring adverse events and by clinical laboratory evaluations. Meta-analytic statistical techniques were used in the combined analysis to establish homogeneity of treatment comparisons across studies. Based on an analysis of patients with baseline ulcer area common to all trials (≤ 10 cm^2), representing 95% of all patients, becaplermin gel-100 μg/g significantly increased ($p = 0.007$) the probability of complete healing compared with placebo gel. It was determined that for the median ulcer area of these patients, which was 1.5 cm^2, the becaplermin gel-100 μg/g treatment group showed a 39% increase in complete healing compared with that of the placebo gel treatment group (50% vs. 36%, respectively, $p = 0.007$). Becaplermin gel-100 μg/g significantly decreased ($p = 0.01$) the time to complete healing compared with placebo gel, with the 35th percentile of time to complete healing being reduced by 30% (14.1 weeks vs. 20.1 weeks, respectively). In patients with ulcers ≤ 5 cm^2 at baseline (a more homogeneous group), becaplermin gel-100 μg/g also significantly increased the incidence of complete healing with a similar decrease in the time to healing. Adverse events reported during treatment or during a 3-month follow-up period were not unexpected for this patient population and were similar in nature and incidence across all treatment groups. We therefore conclude that treatment with becaplermin gel at a dose of 100 μg/g once daily, in conjunction with good ulcer care, is effective and well tolerated in patients with full thickness lower extremity diabetic ulcers. **(WOUND REP REG 1999;7:335–346)**

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AE	Adverse event
ITT	Intent-to-treat
PDGF	Platelet-derived growth factor
rhPDGF-BB	Recombinant human PDGF-BB

Chronic lower extremity diabetic ulcers are a serious and costly complication of diabetes mellitus that negatively affect all aspects of patient quality of life.[1–3] In people with diabetes, neuropathy leads to disruption of the normal architecture of the foot, resulting

in the development of high pressure zones on the plantar surface. These areas of high pressure are particularly susceptible to tissue breakdown and ulcer formation. This condition can be exacerbated by peripheral vascular disease, which afflicts many people with diabetes.[4] At least 15% of people with diabetes will develop ulcers of the lower extremity during their lifetime.[5,6] If not properly treated, these ulcers can become infected or gangrenous and may potentially lead to the amputation of the affected limb.[4] The annual amputation rate among people with diabetes is estimated to be between 41 and 77 per 10,000.[7] In addition to representing a significant economic burden, limb amputation is associated with high morbidity, increased risk of further amputation, and a 5-year mortality rate of 40% to 60%.[5,6]

Platelet-derived growth factor (PDGF) is an approximately 25 kDa dimeric protein composed of two disulfide-linked polypeptide chains.[8,9] It exists in three different isoforms, the heterodimer PDGF-AB, consisting of an A and B chain, and two homodimers, consisting of two A and two B chains, PDGF-AA and PDGF-BB, respectively. The homodimer PDGF-BB has been shown in preclinical studies to promote the formation of granulation tissue at the wound site and to stimulate wound healing.[10]

Becaplermin (recombinant human PDGF-BB [rhPDGF-BB]) is a homodimer produced by recombinant DNA technology by insertion of the gene for the B chain of PDGF into the yeast *Saccharomyces cerevisiae*. The biological activity of becaplermin is similar to that of naturally occurring PDGF and includes promoting chemotactic recruitment and proliferation of cells involved in the wound repair process.

Becaplermin is formulated in a preserved, sodium carboxymethylcellulose-based gel for topical administration. This aqueous gel provides the additional benefit of a moist wound healing environment.[11,12] Becaplermin gel has shown negligible systemic absorption, is well tolerated, and represents an innovative, pharmacologically active treatment for chronic lower extremity diabetic ulcers.

The combined analysis was implemented to synthesize the results of four multicenter, randomized, parallel group studies that evaluated the effects of once-daily topical administration of becaplermin gel on the healing of chronic, full thickness lower extremity diabetic ulcers. The four studies included in this analysis were conducted to compare the efficacy and safety of topically applied becaplermin gel at a dose of 30 μg/g or 100 μg/g with those of placebo gel or good ulcer care alone in the treatment of chronic diabetic ulcers of the lower extremity over a 20-week study period. Treatment arms varied in each study. All patients, regardless of treatment group, received a standardized regimen of good ulcer care. This standardized regimen was chosen, based on recommendations made by wound care subspecialists, to provide patients with the best possible wound care and to limit the potential variability introduced by different methods of wound care.

METHODS

A total of 925 men and women, ranging in age from 23 to 93 years (median age 59 years), with type 1 or type 2 diabetes mellitus were enrolled in the four studies; the intent-to-treat (ITT) population comprised 922 patients. Patients had to have at least one but no more than three (no more than two in Study 4) full thickness (i.e., extending into the subcutaneous tissue and beyond) lower extremity diabetic ulcers that had been present for at least 8 weeks. If more than one lower extremity ulcer was present, the ulcer with the greatest surface area or the ulcer that, in the opinion of the investigator, would take the longest time to heal with good ulcer care alone was designated as the target ulcer. Before randomization, the target ulcer was sharply debrided to remove all nonviable tissue and callus. Any infection or cellulitis present before debridement had to be well controlled before randomization. Transcutaneous oxygen tension had to be ≥ 30 mmHg on the limb of the target ulcer, and the target ulcer had to be free of all necrotic or infected soft and bony tissue after debridement.

Patient exclusion criteria

Patients were excluded if osteomyelitis affecting the area of the target ulcer was present or if the target ulcer was the result of any cause other than diabetes (e.g., electrical, chemical, or radiation insult). Patients with cancer at the time of enrollment were excluded. Additional exclusion criteria included concomitant disease (e.g., connective tissue disease), treatment (e.g., radiation therapy), or medication (e.g., corticosteroids, chemotherapy, or immunosuppressive treatment) that would interfere with the evaluation of study medication. Women who were pregnant or nursing, or of childbearing potential and not using an acceptable method of birth control, were excluded. Patients were required to have a history of compliance and reliability in following study requirements and to give written informed consent before participation in the study. The protocol was approved by the institutional review boards and ethics committees at all study centers.

General study protocol

Eligibility for randomization was determined at visit 1-screening visit, during which a full medical history was obtained and radiographs of the foot at the ulcerated area were taken if necessary. Initial complete sharp debridement of the target ulcer was performed prior to randomization and throughout the study as necessary. In Studies 2–4, more visits included debridements than were done in Study 1. Patients began receiving study medication at visit 2-baseline visit and attended clinic visits weekly through visit 6 and every other week thereafter. Treatment continued for 20 weeks or until complete wound healing was achieved. In the becaplermin gel and placebo gel groups, a thin layer (approximately 1/16 inch) of gel was applied once daily, kept in place for 12 hours with saline moistened gauze, and gently rinsed away before the second dressing change, which also consisted of saline moistened gauze but did not include study medication. In the group receiving good ulcer care alone, dressing changes were performed twice daily with moist saline dressings. Since no study medication was applied in studies that included a treatment arm consisting of good ulcer care alone, these studies were evaluator-blinded such that the individual performing the efficacy assessment was not the same person maintaining the treatment (Table 1). Efficacy and safety evaluations were performed at each visit.

In studies 2, 3, and 4, a follow-up questionnaire was completed at the study site for those patients who healed. The purpose of the questionnaire, which was to be completed 3 months after complete healing was achieved, was to assess the rate of ulcer recurrence and cosmesis of the scar.

General design of studies

Individual study designs are shown in Table 1. Treatment arms in the four studies consisted of two or three of the following regimens. Becaplermin gel (30 μg/g and/or 100 μg/g) plus good ulcer care, placebo gel plus good ulcer care, and good ulcer care alone. The main differences among the studies were the included treatment arms and the entry criteria for baseline target ulcer area (Table 1). The standardized regimen of ulcer care included sharp debridement of ulcers to remove callus, fibrin, and necrotic tissue; moist saline dressing changes every 12 hours; systemic control of infection, if present; glucose control; and off-loading of pressure. Patients were assigned randomly to one of two or three parallel treatment groups depending on the study (Table 1).

Design of individual studies

Results of Studies 1, 2, and 3 have been published previously.[12–15] Study 1 was a phase II multicenter, double-blind, placebo-controlled trial designed to assess the safety and efficacy of becaplermin gel at a dose of 30 μg/g. To be eligible for the study, the target ulcer area had to be between 1 cm^2 and 100 cm^2. A total of 118 patients were randomly assigned to treatment with becaplermin gel-30 μg/g (n = 61) or placebo gel (n = 57). Study 2 was the phase III, pivotal, multicenter, double-blind, placebo-controlled trial that compared the safety and efficacy of becaplermin gel at 30 μg/g or 100 μg/g with those of placebo gel. To be eligible for this study, the patient's target ulcer area had to be between 1 cm^2 and 40 cm^2. A total of 382 patients were randomly assigned to treatment with becaplermin gel-30 μg/g (n = 132), becaplermin gel-100 μg/g (n = 123), or placebo gel (n = 127). The

Table 1. Summary of study designs for all clinical trials

Study No.	Description*	Study design†	Treatment regimens	Number of ITT patients‡	Target ulcer area at baseline (length × width)
1	Phase II safety and efficacy	R, DB, PG	Placebo gel	57	1–100 cm^2
			Becaplermin gel-30 μg/g	61	
2	Phase III safety and efficacy	R, DB, PG	Placebo gel	127	1–40 cm^2
			Becaplermin gel-30 μg/g	132	
			Becaplermin gel-100 μg/g	123	
3	Safety and efficacy, and placebo (vehicle) effect	R, DB/EB§, PG	Good ulcer care alone	68	1–10 cm^2
			Placebo gel	70	
			Becaplermin gel-100 μg/g	34	
4	Safety and efficacy, resource utilization	R, EB, PG	Good ulcer care alone	122	1–40 cm^2
			Becaplermin gel-100 μg/g	128	

*All studies were 20 weeks.

†R = randomized; DB = double-blind; EB = evaluator-blind; PG = parallel group.

‡Intent-to-treat patients were those who received at least 1 dose of study medication and had postbaseline efficacy data.

§Becaplermin and placebo gel treatment arms were double-blinded; the good ulcer care alone arm was evaluator-blinded.

primary objective of Study 3, a multicenter, controlled trial that included 172 patients, was to compare the safety of placebo gel with that of good ulcer care alone. Eligibility criteria included a target ulcer area between 1 cm^2 and 10 cm^2. Patients were randomly assigned to treatment with placebo gel (n = 70) or good ulcer care alone (n = 68). In order to enhance enrollment, this study also included a small (n = 34) becaplermin gel at 100 μg/g arm to offer patients an opportunity to receive active therapy. This active drug treatment arm was not powered for statistical comparison. Study 4, which included 252 patients, was a multicenter, randomized, evaluator-blind, controlled trial designed to assess resource utilization. To be eligible for the study, the patient's target ulcer area had to be between 1 cm^2 and 40 cm^2. The efficacy of becaplermin gel-100 μg/g (n = 128) was compared with that of good ulcer care alone (n = 122).

Except for two patients in Study 4 and one in Study 2 who did not proceed further than signing the consent form, all patients were included in the ITT population. The combined numbers of patients in each ITT treatment group were: becaplermin gel-100 μg/g (n = 285); becaplermin gel-30 μg/g (n = 193); placebo gel (n = 254); good ulcer care alone (n = 190).

Efficacy evaluations

At each visit, the target ulcer was assigned a Functional Assessment score based on whether the ulcer was completely healed without drainage or need of a dressing (scored as 1) or less than completely healed, with drainage and requiring a dressing (scored as 2). The area of the target ulcer was also measured (length × width). Measurements of length, width, and depth were made after debridement, unless debridement of the target ulcer was deemed unnecessary.

The primary efficacy endpoint was complete healing (i.e., Functional Assessment score = 1) within the 20-week study period. A secondary efficacy criterion was the time to achieve complete healing. Patients whose target ulcer did not decrease in area over 2 consecutive visits (Study 1) or did not decrease from baseline by 20% (measured by length times width) at week 10 (Study 2) or 30% by week 8 (Study 4) were considered treatment failures for the purpose of analysis, even if the target ulcer healed later during the study.

Safety evaluations

Safety evaluations over the 20-week study period were based on changes in clinical laboratory results, vital signs, physical examinations, and the incidence of adverse events (AEs), deaths, and premature discontinuations (i.e., before week 20). Adverse events were monitored at each study visit. A treatment-emergent AE was defined as an AE not present at baseline, or if present at baseline, one that worsened in frequency or severity as the study progressed. In addition to these four studies, two additional studies were used in synthesizing safety evaluations. Study 5 involved a single 12-hour application of study therapy, whereas Study 6 was a 28-day study. The total number of patients in both studies combined was 84.

Statistical methods

The primary purpose of this combined analysis was to synthesize the results of the 4 individual studies to more precisely assess the relative efficacies of 4 treatment regimens, with a focus on the comparison of becaplermin gel at a dose of 100 μg/g vs. placebo gel. As noted, the 4 studies were conducted using similar protocols, with the major differences being the treatment doses under study and the allowable ulcer areas at study entry.

Meta-analytic techniques for combining the data across all studies, using individual patient covariate data have been employed in this analysis.[16,17] In particular, the patient's baseline ulcer area was used as a covariate in the analysis, thereby accounting for possible baseline size disparities among treatment groups and across studies.

Of concern in any combined analysis is establishing homogeneity of responses to treatment regimens across the individual studies. In light of the apparent variability of the incidences of complete healing across treatment regimens in the four studies and the varying baseline ulcer area entry criteria, this concern was carefully examined in these analyses through use of suitable logistic regression models and graphical techniques. An initial logistic modeling of the probability of complete healing included terms for study, treatment, and baseline ulcer area, as well as 3 homogeneity contrasts: (i) becaplermin-30 μg/g vs. placebo gel between studies 1 and 2; (ii) becaplermin-100 μg/g vs. placebo gel between Studies 2 and 3; and (iii) becaplermin-100 μg/g vs. good ulcer care alone between Studies 3 and 4. These three homogeneity contrasts were selected to examine the treatment differences that appeared to vary the most across the four studies. The homogeneity analyses were conducted for all ITT patients, all ITT patients with the baseline ulcer area common among all 4 trials (≤ 10 cm^2), and all ITT patients with baseline ulcer area ≤ 5 cm^2. Homogeneity of complete healing

Table 2. Patient demographic characteristics (intent-to-treat population)

Characteristic	Study 1		Study 2		
	Placebo gel (n = 57)	Becaplermin gel 30 μg/g (n = 61)	Placebo gel (n = 127)	Becaplermin gel 30 μg/g (n = 132)	Becaplermin gel 100 μg/g (n = 123)
Sex, n (%)					
Male	46 (80.7)	43 (70.5)	91 (71.7)	82 (62.1)	82 (66.7)
Female	11 (19.3)	18 (29.5)	36 (28.3)	50 (37.9)	41 (33.3)
Race, n (%)					
White	49 (86.0)	53 (86.9)	100 (78.7)	108 (81.8)	101 (82.1)
Nonwhite	8 (14.0)	8 (13.1)	27 (21.3)	24 (18.2)	22 (17.9)
Age (years)					
Mean (SD)	58 (11.9)	63 (11.1)	58 (11.8)	58 (11.3)	57 (11.5)
≤ 60 years, n (%)	34 (59.6)	21 (34.4)	79 (62.2)	76 (57.6)	77 (62.6)
> 60 years, n (%)	23 (40.4)	40 (65.6)	48 (37.8)	56 (42.4)	46 (37.4)
Weight (lbs)					
n*	56	58	126	130	119
Mean (SD)	208 (60.0)	200 (46.0)	217 (56.1)	205 (45.0)	211 (57.8)

*Reduced n values reflect the number of patients with missing baseline data.

Table 2. (continued)

Characteristic	Study 3			Study 4	
	Good ulcer care alone (n = 68)	Placebo gel (n = 70)	Becaplermin gel 100 μg/g (n = 34)	Good ulcer care alone (n = 124)	Becaplermin gel 100 μg/g (n = 128)
Sex, n (%)					
Male	54 (79.4)	49 (70.0)	24 (70.6)	87 (71.3)	91 (71.1)
Female	14 (20.6)	21 (30.0)	10 (29.4)	35 (28.7)	37 (28.9)
Race, n (%)					
White	55 (80.9)	63 (90.0)	28 (82.4)	97 (79.5)	104 (81.3)
Nonwhite	13 (19.1)	7 (10.0)	6 (17.6)	25 (20.5)	24 (18.7)
Age (years)					
Mean (SD)	60 (11.3)	57 (13.0)	59 (11.9)	60 (11.9)	59 (10.8)
≤ 60 years, n (%)	35 (51.5)	41 (58.6)	16 (47.1)	62 (50.0)	70 (54.7)
> 60 years, n (%)	33 (48.5)	29 (41.4)	18 (52.9)	62 (50.0)	58 (45.3)
Weight (lbs)					
n*	65	66	33	118	126
Mean (SD)	215 (56.8)	204 (46.4)	220 (44.3)	213 (44.3)	221 (57.6)

*Reduced n values reflect the number of patients with missing baseline data.

response rates was statistically validated for ITT patients who had baseline ulcer area ≤10 cm^2 (who comprised 95% of the ITT population) and ≤ 5 cm^2 (84% of the ITT population), but could not be validated for the entire ITT population. These analyses confirmed graphic displays of the data that indicated high variability of complete healing response rates for patients with baseline ulcer area > 10 cm^2, possibly attributable to the small sample size in this ulcer area range. Thus, homogeneity of responses among the treatments across the studies was established for ITT patients with baseline ulcer areas ≤10 cm^2 and further logistic linear model fitting was based on this population.

Standard model building techniques for this population yielded a final logistic model including terms for treatment, study, baseline ulcer area (with common slopes for the regimens: becaplermin-100 μg/g gel, becaplermin-30 μg/g and placebo gel, but a separate slope for the good ulcer care alone regimen). Treatment contrasts' levels of significance and estimated probabilities of complete ulcer healing are based on his model. Because the focus was on the comparison of becaplermin-100 μg/g gel to placebo gel, no simultaneous inference adjustments were employed for the quoted significance levels. For clinical comparison of becaplermin 100 μg/g gel to placebo gel, in which the logit scale of the response curves are parallel with respect to baseline ulcer area, the probabilities of complete ulcer healing are necessarily not parallel and relevant differences are expressed, therefore, at the median population ulcer area. All logistic analyses were done using the SAS procedure GENMOD.[18]

Table 3. Baseline target ulcer characteristics (intent-to-treat population)

Characteristic	Study 1		Study 2		
	Placebo gel (n = 57)	Becaplermin gel 30 μg/g (n = 61)	Placebo gel (n = 127)	Becaplermin gel 30 μg/g (n = 132)	Becaplermin gel 100 μg/g (n = 123)
Area (cm^2)					
Mean (SD)	9.0 (16.02)	5.5 (8.46)	2.8 (4.14)	2.6 (2.69)	2.6 (3.41)
≤ 10 cm^2, n (%)	47 (82.4)	55 (90.2)	120 (94.4)	129 (97.7)	118 (95.9)
> 10 cm^2, n (%)	10 (17.5)	6 (9.8)	7 (5.5)	3 (2.3)	5 (4.1)
Duration (weeks)					
n*	57	61	119	123	113
Mean (SD)	77 (81.6)	84 (117.9)	46 (52.1)	56 (80.3)	46 (54.7)
< 8 weeks, n (%)	1 (1.8)	1 (1.6)	2 (1.7)	0	1 (0.9)
≥ 8 weeks, n (%)	56 (98.2)	60 (98.4)	117 (98.3)	123 (100)	112 (99.1)
$TcpO_2$ (mm Hg)†					
n*	40	46	127	132	123
Mean (SD)	59.7 (31.97)	58.6 (34.20)	55.5 (19.61)	54.1 (20.94)	55.0 (22.6)

*Reduced n values reflect the number of patients with missing baseline data.
†Transcutaneous oxygen tension.

Table 3. (continued)

Characteristic	Study 3			Study 4	
	Good ulcer care alone (n = 68)	Placebo gel (n = 70)	Becaplermin gel 100 μg/g (n = 34)	Good ulcer care alone (n = 122)	Becaplermin gel 100 μg/g (n = 128)
Area (cm^2)					
Mean (SD)	2.5 (2.28)	2.2 (2.15)	1.6 (1.41)	2.5 (3.82)	3.2 (4.73)
≤ 10 cm^2, n (%)	68 (100)	69 (98.5)	34 (100)	114 (93.4)	120 (93.7)
> 10 cm^2, n (%)	0	1 (1.4)	0	8 (6.6)	8 (6.2)
Duration (weeks)					
n*	24	24	11	122	128
Mean (SD)	42 (42.0)	53 (60.9)	20 (14.4)	82 (156.6)	59 (72.4)
< 8 weeks, n (%)	0	0	0	0	1 (0.8)
≥ 8 weeks, n (%)	24 (100)	24 (100)	11 (100)	122 (100)	127 (99.2)
$TcpO_2$ (mm Hg)†					
n*	68	70	34	121	125
Mean (SD)	56.5 (24.5)	57.4 (27.5)	49.4 (11.9)	55.9 (18.13)	59.7 (24.49)

*Reduced n values reflect the number of patients with missing baseline data.
†Transcutaneous oxygen tension.

Kaplan-Meier product limit estimators were used for times to complete ulcer healing for ITT patients with baseline ulcer area ≤ 10 cm^2 and ≤ 5 cm^2. Even though the maximum incidence of complete ulcer healing attained was 50% for the becaplermin-100 μg/g gel regimen, the maximum healing rate in the placebo gel group was 35%, therefore the 25th and 35th percentiles were used to summarize time to healing. Inferences comparing times to complete ulcer healing were conducted using Cox's proportional hazards model with terms for treatment, study, and baseline ulcer area.

Limited statistical results are provided for the individual studies. The methods for obtaining the quoted levels of the significance are briefly stated, and more detailed descriptions of the statistical methodologies for the individual studies can be found in their respective cited publications.

RESULTS

The combined ITT population consisted of 922 patients. Patient demographic and baseline characteristics were similar across treatment groups within studies and across studies with one exception (Tables 2 and 3). The ulcer areas in Study 1 were larger overall than the other three studies because the entrance criteria allowed for a minority of patients to enter with larger ulcer areas. In addition, a different method was used for measuring ulcer area in this study, in which a formula based on an assumed circular shape and the calculated radius based on ulcer

Tabl 4. Percent of patients completing each study (intent-to-treat population)

	Study number			
	1	2	3	4
n	118	382	172	252
Completions (%)	80	81	76	88
Total discontinuations (%)	20	19	24	12
Discontinuations because of adverse events (%)	12	11	17	4

maximal dimensions provided the area at each visit. The other studies utilized planimetric analysis of ulcer tracings, typically resulting in smaller and more precise measurements. In all four studies, the majority of patients completed the study (Table 4).

Homogeneity of treatment responses

Homogeneity of treatment responses across the four studies was established ($p = 0.135$, not significant at the 0.10 level) for the ITT population with baseline ulcer area ≤ 10 cm^2. This population (874 patients) represents 95% of the original ITT population (922 patients). Subsequent analyses are based on this population of 874 patients. Although the statistical criteria for combining studies were met for patients with ulcers with baseline areas ≤ 10 cm^2, the group of patients with ulcers ≤ 5 cm^2 (774 patients or 84% of the ITT) was even more homogeneous in response to treatment.

Combined analysis of treatment efficacy

Of the 922 patients in the ITT population, 874 (95%) had baseline ulcer areas ≤ 10 cm^2 and were included in this analysis. Analytical and graphic statistical methods showed homogeneity of treatment responses for this population. Based on patients with baseline ulcer area ≤ 10 cm^2, the estimated probability of complete healing was significantly higher ($p = 0.007$; logistic regression model) with becaplermin gel at a dose of 100 μg/g treatment compared with placebo gel treatment, regardless of baseline ulcer area (≤ 10 cm^2) (Figure 1). For the median baseline ulcer area of 1.5 cm^2, the becaplermin gel-100 μg/g treatment group showed a 39% increase in complete healing compared with that of the placebo gel treatment group (50% vs. 36%, respectively) (Figure 2). Although the estimated probability of complete healing in patients treated with becaplermin gel at 30 μg/g was not statistically different from that in patients treated with placebo gel, it was numerically greater (42% vs. 36%, respectively). This effect increased with concentration, such that the treatment effects at the median baseline ulcer area were ordered: becaplermin gel-100 μg/g > 30 μg/g > placebo gel > good ulcer care alone.

Treatment with becaplermin gel at a dose of 100 μg/g significantly ($p = 0.010$; Cox proportional

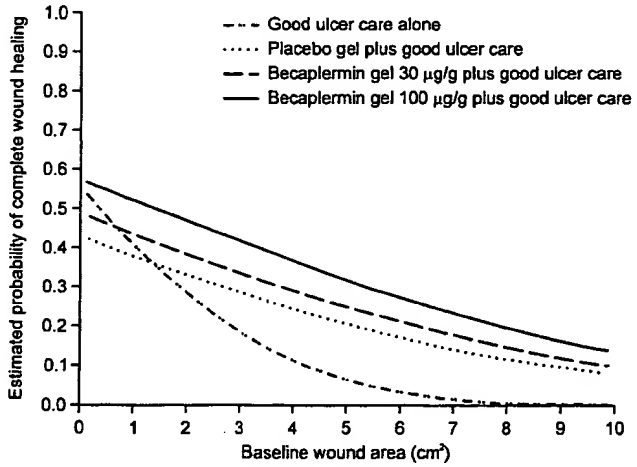

Figure 1. Estimated probability of complete healing in patients with baseline ulcer area ≤ 10 cm^2 (≤ 14 cm^2 measured by length times width). A significantly higher estimated probability ($p = 0.007$) was calculated based on a logistic regression analysis.

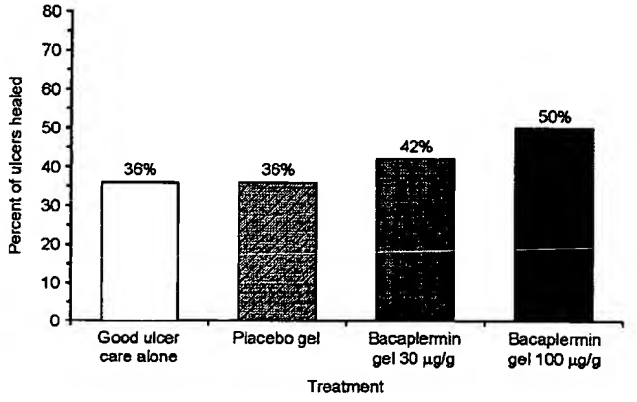

Figure 2. Estimated incidence of complete healing in the combined analysis. Estimates are based on the statistical model, baseline ulcer area ≤ 10 cm^2, and median ulcer size 1.5 cm^2.

hazards model) decreased the time to achieve complete healing, with the 35th percentile of time to achieve complete healing 30% less in becaplermin gel-100 μg/g compared with placebo gel (14.1 weeks vs. 20.1 weeks, respectively; Kaplan-Meier estimates) (Table 5). Life table estimates and estimated values of the incidence of complete healing are shown in Table 6, Table 7, and Figure 3. Similar analyses were performed for ulcers with baseline area ≤ 5 cm^2—the most homogeneous group. Superiority of becaplermin gel-100 μg/g compared with placebo gel was again showed for both incidence of and time to healing (Table 8).

In the becaplermin treatment groups, most patients experienced a reduction in ulcer size relative to baseline. A small percentage of patients experienced a worsening of their ulcers. In fact, 15% of becaplermin gel-100 μg/g and 22% of the becaplermin gel-30 μg/g treated ulcers showed an increase in size relative to baseline. Moreover, many of the ulcers that increased in relative area had small areas at baseline and therefore had greater potential for measurement error to play a role in the precision with which ulcer size could be measured.

Efficacy results of individual studies

In the four individual efficacy trials, the observed overall incidence of complete healing in the ITT population is shown in Figure 4. Essentially identical results were obtained for the population with baseline ulcer areas ≤ 10 cm^2. In Study 1, the overall incidence of complete healing in all ITT patients treated with becaplermin gel-30 μg/g was 48% vs. 25% for those treated with placebo gel ($p = 0.02$, logistic regression analysis; 49% vs. 28%, respectively, for ulcers with baseline areas ≤ 10 cm^2).[13] In Study 2, the overall incidence of complete healing in all ITT patients receiving becaplermin gel at a dose of 100 μg/g was 50% vs. 36% and 35% for those receiving becaplermin gel-30 μg/g and placebo gel, respectively.[14] Only becaplermin gel at 100 μg/g was significantly different from placebo gel ($p = 0.01$, logistic regression analysis with one-sided test at the

Table 5. Kaplan-Meier estimates* of weeks to complete ulcer healing

	Good ulcer care alone	Placebo gel	Becaplermin gel 30 μg/g	Becaplermin gel 100 μg/g
n	182	236	183	272
25th percentile (weeks)	12.1	14.0	12.4	10.1†
35th percentile (weeks)	> 20.1	20.1	16.3	14.1†

Based on all ITT patients with baseline ulcer area ≤ 10 cm^2 measured by planimetry (≤ 14 cm^2 measured length × width).

* 25th and 35th percentiles are Kaplan-Meier estimates. Fewer than 35% of patients treated with good ulcer care alone achieved complete healing by 141 days, hence the 35th percentile for this group is listed simply as being > 20.1 weeks.

†$p = 0.010$, becaplermin gel-100 μg/g vs placebo gel; Cox's Proportional Hazards Analysis.

Table 6. Estimated values for incidence of complete healing‡

Baseline ulcer area (cm^2)	Good ulcer care alone	Becaplermin gel			Difference*	Relative difference†
		Placebo gel	30 μg/g	100 μg/g		
1	41.7	38.5	44.0	52.6	14.1	36
1.5 (median)	35.5	36.3	41.6	50.2	13.9	38
2	28.9	33.8	39.0	47.5	13.7	40
3	18.7	29.3	34.2	42.4	13.1	45
4	11.6	25.3	29.8	37.5	12.2	48
5	6.9	21.6	25.7	32.8	11.2	52
6	4.0	18.3	21.9	28.4	10.1	55
7	2.3	15.4	18.6	24.4	9.0	58
8	1.3	12.9	15.7	20.8	7.9	61
9	0.8	10.8	13.2	17.7	6.9	64
10	0.4	9.0	11.0	14.9	5.9	66

Based on all ITT patients with baseline ulcer area ≤ 10 cm^2 measure by planimetry (≤ 14 cm^2 measured by length × width).

* Becaplermin gel-100 μg/g – placebo gel.

†100% × [(becaplermin gel-100 μg/g – placebo gel) ÷ placebo gel].

‡All values given as percent.

Tabl 7. Life table estimates* of the incidence of complete healing over time for all 4 studies†

	Treatment	
Time (wk)	Becaplermin gel 100 μg/g	Placebo gel
2	0	0
4	4	3
6	7	5
8	14	12
10	20	16
12	27	22
14	33	24
16	39	29
18	42	31
20	45	34

* Based on all ITT patients with baseline ulcer area ≤ 10 cm^2.
†All values given as percent

0.025 level of significance; 51% vs. 36% vs. 35%, respectively, for ulcers with baseline areas ≤ 10 cm^2). In Study 3, which was designed to compare placebo gel with good wound care alone, the overall incidence of complete healing in all ITT patients was 44% for patients receiving becaplermin gel-100 μg/g compared with 36% for those receiving placebo gel and 22% for those receiving good ulcer care alone (44% vs. 35% vs. 22%, respectively, for ulcers with baseline areas ≤ 10 cm^2)[12] In Study 4, the difference in the overall incidence of complete ulcer healing (ITT patients) in the becaplermin gel-100 μg/g arm (36%) and the good ulcer care alone arm (32%; 38% vs. 32%, respectively, for ulcers with baseline areas ≤ 10 cm^2) was not statistically significant.

Incidence of ulcer recurrence

The clinical studies also included a 3-month follow-up period during which no standardized regimen of preventive footwear or foot care was implemented. The incidence of ulcer recurrence was 28% to 29% in all treatment groups.

Safety results from all studies

The results presented in this section include safety data from the four studies synthesized for efficacy, as well as two smaller studies. A total of 1006 patients were evaluated for safety. The safety analysis included patients treated with becaplermin gel at a dose of 100 μg/g, as well as patients treated with becaplermin gel at all doses. Many of the treatment-emergent AEs reported were related to the lower extremity ulcer(s) and the underlying disease state (diabetes mellitus) of the patients and were similar in incidence and severity across all treatment groups. The most common AEs were infection, cellulitis, skin ulceration, and osteomyelitis. Treatment-emergent AEs experienced by ≥ 5% of all patients are presented in Table 9.

The most frequently reported serious adverse events (SAEs) involved body systems commonly affected in patients with diabetes or sequelae of nonhealing diabetic ulcers. The incidence of SAEs was

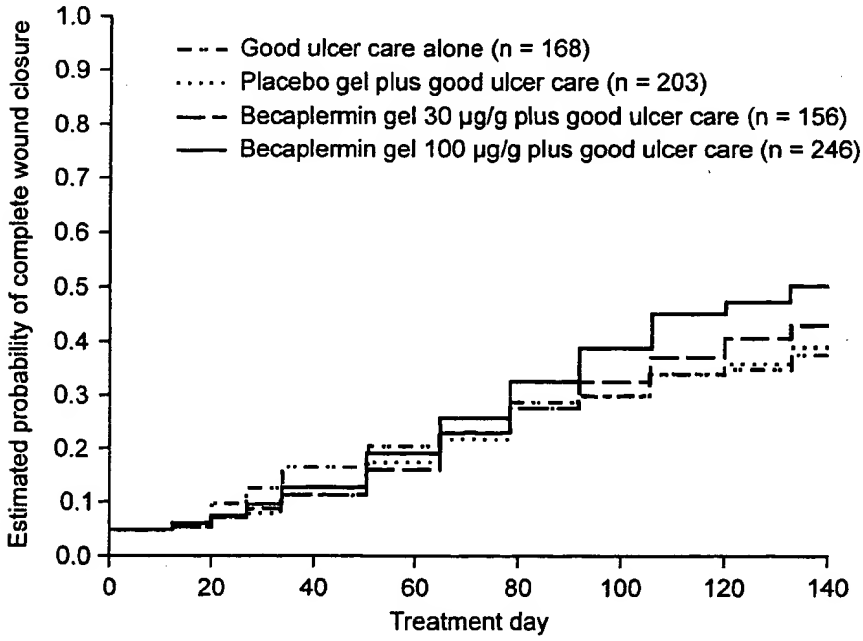

Figure 3. Life table estimates of the time to complete healing (baseline ulcer area ≤ 10 cm^2; ≤ 14 cm^2 measured by length times width). A significantly higher estimated probability ($p = 0.015$) was calculated for becaplermin gel at a dose of 100 μg/g vs. placebo gel, based on Cox's proportional hazards model.

Table 8. Summary of efficacy results for patients with baseline ulcer area ≤ 5 cm^2

	Good ulcer care alone	Placebo gel	Becaplermin gel 30 μg/g	Becaplermin gel 100 μg/g	Difference (100 μg/g–placebo)	Relative difference
n	168	203	157	246		
Incidence of complete healing, n (%)	51 (30.4)	71 (35.0)	65 (41.4)	115 (46.7)*	–	–
Estimated incidence (%) of complete healing at endpoint for baseline ulcer area (cm^2)						
1	41.8	38.9	45.0	53.1	14.2	37
1.25 (median)	36.5	37.1	43.1	51.2	14.1	38
2	22.9	32.2	37.8	45.7	13.5	42
3	11.0	26.1	31.2	38.8	12.5	48
4	4.9	20.8	25.2	31.9	11.1	53
5	2.1	16.4	20.1	25.8	9.4	57
Kaplan-Meier estimates of days to complete healing						
25th percentile	85	84	86	71†	–	–
35th percentile	141	131	113	92†	–	–
					–	–

* Statistically superior to placebo gel; $p = 0.009$, combined logistic regression analysis.

† Time to healing significantly shorter than in the placebo group ($p = 0.008$; combined Cox's Proportional Hazards Analysis).

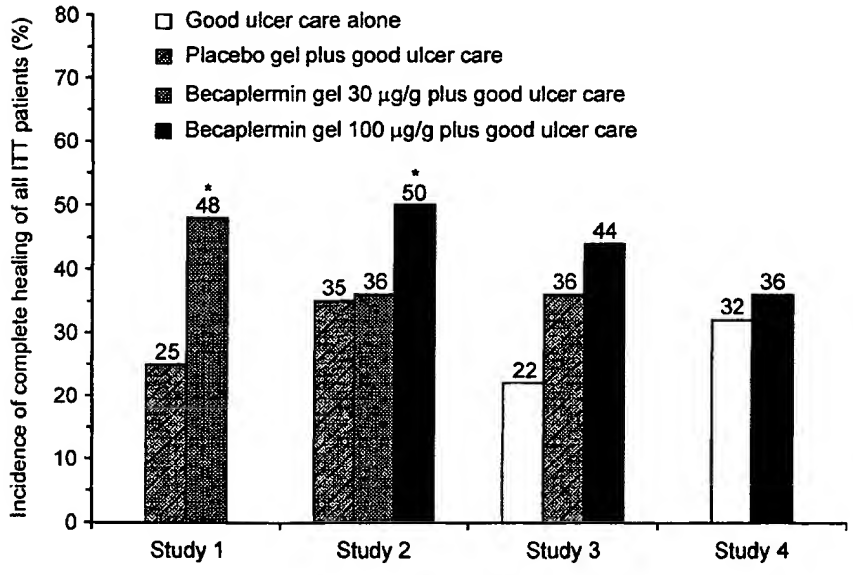

Figure 4. Overall incidence of complete healing of all ITT patients in 4 randomized clinical trials of becaplermin gel. *$p < 0.05$ vs. placebo gel.

24% for the becaplermin gel treatment group, 25% for the placebo gel treatment group, and 28% for the group treated with good ulcer care alone. The majority of SAEs were considered to be unrelated to study medication; however, some wound infection–related SAEs were considered by the investigator as possibly related to treatment.

Most of the patients enrolled in these studies completed treatment; however, 9% of patients receiving becaplermin gel, 11% of patients receiving placebo gel, and 11% of patients receiving good ulcer care alone discontinued because of an AE. Infection, cellulitis, and osteomyelitis were the AEs that most frequently led to discontinuation of treatment.

Thirty-seven patients, including 21 (4%) treated with becaplermin gel, 9 (3%) treated with placebo gel, and 7 (4%) treated with good ulcer care alone, died during or soon after the study. The majority of deaths were related to the patients' underlying diabetes. No deaths were considered related to study medication.

Table 9. Treatment-emergent adverse events reported by ≥ 5% of patients*

	Treatment group			
Body/system disorders	**Good ulcer care alone**	**Placebo gel**	**Becaplermin gel 100 μg/g**	**Becaplermin all doses combined**
n	190	275	177	407
Skin and appendages	39†	21	30	25
Resistance mechanism	35	24	26	24
Body as a whole-general	33	25	24	21
Application site	16	14	13	12
Respiratory system	20	13	14	11
Gastrointestinal system	18	10	15	12
Musculoskeletal system	16	9	15	10
Central and peripheral nervous system	9	5	8	7
Vascular (extracardiac)	7	3	3	5
Cardiovascular, general	6	5	5	5
Urinary system	5	6	6	5
Psychiatric	4	3	5	4

* For all patients entered into the four 20-week studies and two additional blinded studies of shorter duration.
†Values given as percent.

DISCUSSION

The effect of a single recombinant growth factor, rhPDGF-BB (becaplermin), in promoting wound healing in patients with nonhealing lower extremity diabetic ulcers was evaluated in this analysis. Becaplermin is the first growth factor to show a statistically significant effect in both phase II and phase III clinical trials.[13,14]

Meta-analytic statistical techniques justified a combined analysis of four studies of patients within the ulcer area common to all trials (≤ 10 cm^2) by establishing statistical homogeneity of treatment comparisons across the four studies for this population. This analysis showed that administration of becaplermin gel at a dose of 100 μg/g, in conjunction with a standardized regimen of good ulcer care, increased the probability of achieving complete healing with estimated incidences at the median baseline ulcer size of 1.5 cm^2 by 39% compared with placebo gel. The probability of healing in the becaplermin gel-100 μg/g was also higher compared with good ulcer care alone. Although there was no statistically significant effect with becaplermin gel at 30 μg/g, the overall incidence of complete healing in this group was numerically higher than that in either the placebo gel group or the group treated with good wound care alone. This finding is consistent with a concentration-related effect of becaplermin gel. The time to complete healing was also significantly shorter in the becaplermin-100 μg/g gel group compared with the placebo gel group.

The incidence of ulcer recurrence, assessed 3 months after healing in all studies, was the same in all treatment groups, showing that the durability of healed ulcers was comparable in all treatment groups. AEs reported in these studies were not unexpected for this patient population and were similar in nature and incidence across all treatment groups.

Study 2, the pivotal clinical study, showed superior efficacy of becaplermin gel-100 μg/g compared with placebo gel.[14] The results of the combined analysis confirm this finding.

The results of this analysis suggest that, within the setting of a comprehensive wound management program, treatment with becaplermin gel at a dose of 100 μg/g once daily increases the incidence of complete healing. Becaplermin gel has an excellent safety profile, is well tolerated, and is easily used by patients or caregivers outside a clinical setting. Future studies are underway to assess the efficacy and safety of becaplermin gel in other types of chronic wounds and to quantitate and assess the influence of different factors (e.g., target ulcer size, depth, duration, etc.) on wound healing. Additional studies designed to address issues such as the impact of the treatment on the quality of life of people with lower extremity diabetic ulcers and cost-effectiveness are also ongoing.

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